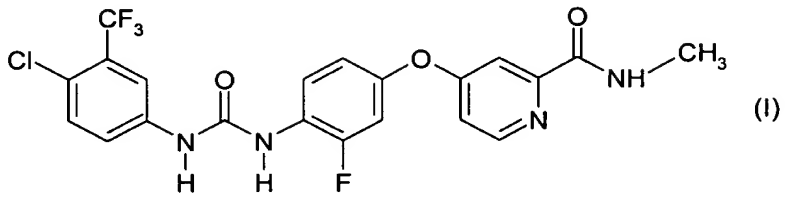
1. A compound of Formula (I) or a salt, or a prodrug or a metabolite or an isolated stereoisomer thereof



(I)

2. A pharmaceutically acceptable salt of a compound of Formula I of claim 1 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

3. A compound which is 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide, or a salt thereof.

4. A pharmaceutically acceptable salt of a compound of claim 3 which is a basic salt of an organic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid

(tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid.

5. A compound which is which is a hydrochloride, benzenesulfonate, or methanesulfonate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-2-fluoro-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

6. A pharmaceutical composition comprising a compound of claim 1 and a physiologically acceptable carrier.

7. A pharmaceutical composition comprising a compound of claim 3 and a physiologically acceptable carrier.

8. A pharmaceutical composition for the treatment of a disease in a human or other mammal regulated by a protein kinase, associated with an aberration in the protein kinase signal transduction pathway comprising a compound of claim 1 and a physiologically acceptable carrier.

9. A pharmaceutical composition for the treatment of a hyper-proliferative disorder comprising a compound of claim 1 and a physiologically acceptable carrier.

10. A pharmaceutical composition for the treatment of a cancerous cell growth comprising a compound of claim 1 and a physiologically acceptable carrier.

11. A pharmaceutical composition which comprises a pharmaceutically acceptable salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-2-fluoro-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea and a physiologically acceptable carrier.

12. A method for regulating tyrosine kinase signal transduction comprising administering to a human or other mammal a compound of claim1.

13. A method for treating or preventing a disease in a human or other mammal which is regulated by tyrosine kinase and associated with an aberration in the tyrosine kinase signal transduction pathway, said method comprising administering to a human or other mammal a compound of claim 1.

14. A method for treating or preventing a disease in a human and/or other mammal which is a VEGFR-2 mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

15. A method for treating or preventing a disease in a human and/or other mammal which is a PDGFR mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

16. A method for treating or preventing a disease in a human or other mammal which is a raf-mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

17. A method for treating or preventing a disease in a human or other mammal which is a p38-mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

18. A method for treating or preventing a disease in a human or other mammal which is a VEGF-mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

19. A method for treating or preventing a disease in a human or other mammal which is a hyper-proliferative, inflammatory and/or angiogenesis disorder which comprises administering to a human or other mammal a compound of claim 1.

20. A method for treating or preventing a disease in a human or other mammal which is a hyper-proliferative disorder which comprises administering to a human or other mammal a compound of claim 1.

21. A method as in claim 20, wherein the hyper-proliferative disorder is cancer.

22. A method as in claim 21, wherein said method comprises administering to a human or other mammal a compound of claim 1 in combination with one or several additional anti-cancer agents.

23. A method for treating or preventing a disease in a human or other mammal characterized by abnormal angiogenesis or hyperpermiability processes comprising administering to a human or other mammal a compound of claim 1.

24. A method as in claim 23, for treating or preventing a disease in a human or other mammal characterized by abnormal angiogenesis or hyperpermeability processes, comprising administering to a human or other mammal, a compound of claim 1 simultaneously with another anti-angiogenesis agent, either in the same formulation or in separate formulations.

25. A method for treating or preventing one or more of the following conditions in humans and/or other mammals:

tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis, rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, cornal ulceration, proteinuria and coronary thrombosis from atherosclerotic plaque, aneurismal aortic, birth control, dystrophobic epidermolysis bullosa, degenerative cartilage loss

following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease or demyelating disease of the nervous system,

said method comprising administering to a human or other mammal, a compound of claim 1.

26. A method for treating or preventing one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis;

in combination with another condition selected from the group consisting of:

rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Krohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (Plasmodium falciparum malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelation and oligiodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) and complications due to total hip replacement,

said method comprising administering to a human or other mammal a compound of claim 1.

27. A method for treating or preventing one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis,

psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis,

in combination with an infectious disease selected from the group consisting of :

tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV);

said method comprising administering to a human or other mammal a compound of claim 1.

28. A method as in claim 22 wherein the additional anti-cancer agent is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine, oxaliplatin, gemcitabine, capecitabine, epothilone and its natural or synthetic derivatives, tositumomab, trabedectin, and temozolomide. trastuzumab, cetuximab, bevacizumab, pertuzumab, ZD-1839 (Iressa), OSI-774 (Tarceva), CI-1033, GW-2016, CP-724,714, HKI-272, EKB-569, STI-571 (Gleevec), PTK-787, SU-11248, ZD-6474, AG-13736, KRN-951, CP-547,632, CP-673,451, CHIR-258, MLN-518, AZD-2171, PD-325901, ARRY-142886, suberoylanilide hydroxamic acid (SAHA), LAQ-824, LBH-589, MS-275, FR-901228, bortezomib, and CCI-779.

29. A method as in claim 22 wherein the additional anti-cancer agent is a cytotoxic agent selected from the group consisting of DNA topoisomerase I and II inhibitors, DNA intercalators, alkylating agents, anti-metabolites, cell-cycle blockers, microtubule disruptors, and Eg5 inhibitors.

30. A method as in claim 22 wherein the additional anti-cancer agent is selected from the group consisting of inhibitors of growth factor receptor signaling, histone deacetylase inhibitors, inhibitors of the PKB pathway, inhibitors of the Raf/MEK/ERK pathway, inhibitors of the mTOR pathway, and proteasome inhibitors.

31. A method for treating or preventing one or more of the following conditions in humans and/or other mammals:

rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Krohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (Plasmodium falciparum malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelation and oligiodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement,

said method comprising administering to a human or other mammal, a compound of claim 1.

32. A method for treating or preventing one or more of the following conditions in humans and/or other mammals:

tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV) ,

said method comprising administering to a human or other mammal, a compound of claim 1.

33. A method for treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of cancer, in a human and/or other mammal by administering an effective amount of a compound of claim 1 to said mammal.

34. A method for treating or preventing cancer in a human or other mammal which comprises administering to a human or other mammal a single active principle combining inhibition of tumor cell proliferation mediated by the raf / MEK / ERK pathway, and inhibition of angiogenesis mediated by PDGF and VEGF.

35. A method of claim 34 where said inhibition of tumor cell proliferation is caused by inhibition of raf kinase, and said inhibition of angiogenesis is caused by dual inhibition of PDGFR-beta and VEGFR-2 kinases.

36. A method for treating or preventing cancer in a human or other mammal which comprises administering to a human or other mammal a single active principle combining inhibition of tumor cell proliferation mediated by the raf pathway, and inhibition of angiogenesis mediated by PDGF or VEGF.

37. A method of treating and/or preventing a disease and/or condition in a subject in need thereof, comprising administering an effective amount of a compound of ~~claim 1 or 2~~ Claim 1.

38. A method of claim 37, wherein said method comprises causing tumor regression in a subject or cells therefrom.

39. A method of claim 37, wherein said method comprises inhibiting lymphangiogenesis.

40. A method of claim 37, wherein said method comprises inhibiting angiogenesis.

41. A method of claim 37, wherein said method comprises inhibiting lymphangiogenesis and angiogenesis.

42. A method of claim 37, wherein said method comprises stimulating the proliferation of hematopoietic progenitor cells.

43. A method of claim 37, wherein said method comprises treating a disorder in a mammalian subject mediated by raf, VEGFR-2, VEGFR-3, PDGFR-beta, p38 and/or flt-3.

44. A method of claim 37, wherein said method comprises determining whether a condition can be modulated by said compound, comprising measuring the expression or activity of raf, VEGFR-2, VEGFR-3, PDGFR-beta, p38 and/or flt-3, in a sample comprising cells or a cell extract, wherein said ample is obtained from a subject or cell having said condition, whereby said condition can be modulated by said compound when said expression or activity is different in said condition as compared to a normal control.

45. A method of claim 44, further comprising comparing the expression in said sample to said normal control.

46. A method of claim 37, wherein said method comprises assessing the efficacy of said compound disorder, comprising administering said compound, measuring the expression or activity of raf, VEGFR-2, VEGFR-3, PDGFR-beta, p38, and/or flt-3, and determining the effect of said compound on said expression or activity.

47. A method of claim 37, wherein said method comprises determining the presence of raf, VEGFR-2, VEGFR-3, PDGFR-beta, p38 and/or flt-3 in a sample of a biological material, contacting said sample with said compound, and determining whether said compound binds to said material.

48. A method of claim 37, wherein said method comprises treating a tumor in a subject in need thereof, comprising administering an effective amount of said compound wherein said amount is effective to inhibit tumor cell proliferation and neovascularization.

49. A compound which is a naturally occurring metabolite of the compound of claim 3.

50. A compound of claim 49 where the metabolism site is either one of the two urea nitrogen atoms, or the pyridine nitrogen atom, or the methylamide functionality, or any combination of the above.

51. A compound of claim 49 where either urea nitrogen atom carries a hydroxyl group, and/or the pyridine nitrogen atom is oxidized, and/or the amide functionality is de-methylated.

52. A compound of claim 49 which is selected from:
4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid amide,
4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-1-hydroxy-pyridine-2-carboxylic acid methylamide, or
4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-1-hydroxy-pyridine-2-carboxylic acid amide.

53. A method as in claim 19, where the inflammatory disorder is selected from rheumatoid arthritis, COPD, Crohn's disease and proriasis.

54. A method for treating or preventing a disease in a human or other mammal which is a flt-3 mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.